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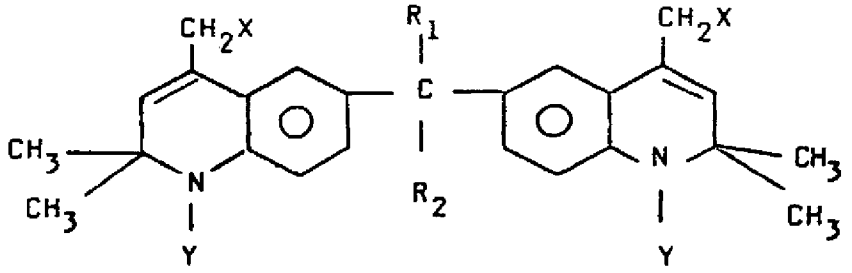

(I)

(57) Abstract

There are provided new compounds of general formula (I) obtained by the condensation of 2,2,4-trimethyl-1,2-dihydro-quinoline or salts thereof with an oxo derivative of the general formula R_1R_2CO, wherein R_1 stands for optionally substituted C_{1-4} alkyl and R_2 stands for optionally substituted C_{1-2} alkyl, X stands for hydrogen or SO_3Me, wherein Me stands for hydrogen, alkali or alkali earth metal ion, Y stands for hydrogen or acyl. The new compounds can be used as antioxidants, and particularly for increasing coccidiostatic effect.

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CONDENSATION PRODUCTS OF 2,2,4-TRIMETHYL-1,2-DIHYDRO-QUINOLINE AND OXO COMPOUNDS AND DERIVATIVES THEREOF

The present invention relates to new condensation products of 2,2,4-trimethyl-1,2-dihydro-quinoline with oxo compounds and the derivatives of same as well as a process for the preparation thereof and fodders and fodder premixes containing said compounds as well as pharmaceutical compositions containing as active ingredient the new compounds.

In the last decades the significance of the use of antioxidants has increased all over the world in various fields and consequently, the use of the antioxidants has been widely spread. Antioxidants are most often used in rubber industry and in plastic industry and in this field the highest requirement is the specific effectivity of the antioxidants and in addition a very important factor is compatibility as well as small sensibility to migration etc. The use of antioxidants in agriculture, food industry and recently in veterinary science and human therapy has increased significantly. While in rubber and plastic industry several amine and phenol type antioxidants are used for the stabilization of fodders, practically only 6-ethoxy-1,2-dihydro-2,2,4-trimethyl-quinoline (EMQ) and 2,6-di-tertiary butyl-hydroxy-toluene (BHT) have been used. The antioxidants suitable for the stabilization of fodder mixtures have to meet simultaneously several essential requirements, such as wide spectrum, low toxicity, respective no damage in optimal case. The last point of view is considered in the recommendation of

WHO/FAO Nutrition Meeting Series No. 40 A, B, C, WHO/FOD AU 67.29, according to which such antioxidants should be used for the mentioned purposes, the LD_{50} value of which exceeds 5 g/kg body weight. It is known that either EMQ nor BHT meets this requirement. In spite of this fact these two compounds have been most accepted according to the present state of art. These two compounds are the best in meeting said complex requirements.

6,6'-methylene-bis(2,2,4-trimethyl-1,2-dihydro-quinoline) is rather used in human therapy due to its radio-sensibilizing properties and it has proved to be really suitable for the stabilization of fodders as due to the extreme sensibility of its methylene group very often a colourization occurred in the fatty tissue of the animals.

The antioxidant activity of 6,6'-ethylydene-bis(2,2,4-trimethyl-1,2-dihydro-quinoline) called as XAX-M is suitable, its toxicity is low, but upon oxidation the ethylydene group is also oxidized and has a certain colourizing effect.

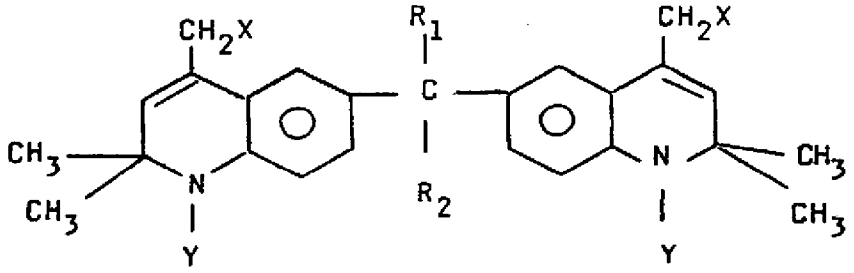
A further disadvantage of XAX-M prepared according to Hungarian patent specification No. 162,358 is that the product is not homogeneous chemically, but according to page 4 of the Hungarian patent specification the polycondensation degree, i.e. the number of dihydro-quinoline units changes depending upon the reaction conditions. The products obtained by acetaldehyde or higher aldehyde condensation form a mixture of condensed molecules containing 2 to 4 dihydro quinoline units. A constant composition cannot be easily ensured, although this is required by the user.

No economic and in practice applicable process has been found so far. DOS 35 40 105 relates to the same product and to its property increasing the coccidiostatic activity of known coccidiostatics.

The present invention was aimed to find a new compounds reserving the good antioxidant activity of the known dihydro-quinoline derivatives, but simultaneously to obtain a new product of chemically homogeneous structure being suitable for human and veterinary use increasing the activity of coccidiostatics and showing low toxicity. The new compounds should be prepared by an economic technology in high purity.

We have now found that new compounds meeting the above requirements can be prepared if 2,2,4-trimethyl-1,2-dihydro-quinoline is condensed under special reaction conditions with lower ketones and if desired the obtained compounds are sulfonated and/or acylated.

According to the present invention new compounds of the general Formula (I)



and acid addition salts thereof are prepared - wherein

R^1 stands for optionally substituted C_{1-4} alkyl and

R^2 stands for optionally substituted C_{1-2} alkyl,

X stands for hydrogen or SO_3Me - wherein

Me stands for hydrogen, alkali or alkali earth metal ion,

Y stands for hydrogen or acyl.

The new compounds can be prepared by condensing aceto-anil (2,2,4-trimethyl-1,2-dihydro-quinoline) or salts thereof with an oxo derivative of the general Formula R^1R^2CO - wherein R^1 and R^2 are as defined above, in the presence of 1-5 %, preferably 2-3 % nitrogen containing base as a cocatalyst, preferably triethanol amine, pyridine or anyline and in the presence of a mineral acid, preferably 0.9-2.5 mole, preferably 1.25-1.75 mole hydrochloric acid as a catalyst related to the dihydro quinoline in a solvent and if desired converting the obtained product to acid addition salt or setting free the free base from the salt and if desired sulfonating and/or acylating the obtained base with sulfuric acid or oleum.

The acid addition salts can be formed with an acid, such as hydrochloric acid, hydrogen bromide or sulfuric acid, preferably hydrochloric acid.

In the meaning of R^1 the alkyl groups can be straight or branched and can stand for an optionally substituted C_{1-4} alkyl, preferably methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec.butyl, preferably methyl, ethyl or isobutyl. The substituents can be selected from hydroxyl, halogen, C_{1-4} alkoxy, carboxyl and C_{1-4} alkoxy-carbonyl. R^2 may preferably stand for C_{1-2} alkyl, preferably methyl, ethyl, which can be substituted with the same groups as given for R^1. X preferably stands for hydrogen or SO_3Me, wherein Me stands for alkali or alkali earth metal ion, preferably sodium, potassium or

calcium ion. Y preferably stands for hydrogen or an acyl group, preferably acetyl, formyl, benzoyl, particularly acetyl.

Surprisingly the use of a nitrogen containing base results in a quick condensation and thus the formation of side products is eliminated.

In the course of condensation the reaction medium is the ketone itself in an amount of 0-40 % containing preferably 10-20 % of water.

Sulfonation can be carried out by methods known per se using oleum or sulfuric acid. Acylation can be performed with known acylating agents such as acetic anhydride, acetyl chloride, benzoyl chloride, formyl chlorice etc.

The reaction mixture can be worked up by filtering the salt, preferably the hydrochloride and by centrifuging and converting it into free base. A product of a purity higher than 95 % is obtained. According to another method the product is worked up together with the mother liqueur, whereafter the unreacted starting material is distilled off in vacuo and thus a product of 60-80 % purity is obtained. It shows that a pure product is obtained without crystallization. The reaction is carried out at a temperature ranging from room temperature to the boiling point of the mixture, optionally under pressure.

As a ketone preferably acetone, methyl ethyl ketone or methyl isobutyl ketone, particulary acetone is used. The molar ratio of the reactant related to acetoanil is generally ranging from 0.5 mole to a several fold excess. Preferably a 10 fold excess, is used.

The other starting material used according to the invention is 2,2,4-trimethyl-1,2-dihydro-quinoline and the compound is known from Bayer, J. Prakt. Chem. 2/33, 401/1886, and Combes, Bull. Soc. Chim. Fr. 49, 89 (1888).

The ketone condensation products of the invention are novel compounds. Due to their chemical structure they do not show a colourizing effect and can be used in a wide spectrum as antioxidant in the field of industry, food industry and fodder industry as well as in the field of therapy and veterinary science. The property of the new compounds by which they increase the activity of known coccidiostatics is particularly significant.

We have found for instance that 2,2-di(2',2',4'-trimethyl-1',2'-dihydroquinolin-6'-yl)-propane shows an excellent rubber antiageing activity and does not cause colouration. Similarly 2,2-di(2',2',4'-trimethyl-1',2'-dihydro-quinoline)-butane can be used as a non-colourizing rubber antiageing agent as it is dissolved extremely well in rubber mixtures and it can be administered even at 5 % to products being contact with food.

2,2-di(2',2'-dimethyl-4'-sodium-methane sulfonate-1',2'-dihydroquinolin-6'-yl)-propane is well soluble in water and can be consequently well applied in the form of injection in human therapy. The compound prevents the organism from detrimental free radical reactions. This is significant in case of poisoning, radiation injuries and disturbances of the circulation. In veterinary therapy encelophalomalatia in

poultry keeping can be treated when administered the compound into the drinking water.

Out of the tested new antioxidant active ingredients the toxicity of 2,2-di(2',2',4'-trimethyl-1,2',2'-dihydro-quinoline)-propane is very low and it can be well applied for foddering, and food industrial and therapeutical purposes and for stabilizing organisms, as well as in animal fodders, especially as antioxidants in poultry, rabbit and pig fodders and as activity increasing components of cocciodiostatics. Even under extreme conditions (in the presence of iron, copper compounds or halides) no decolourization occurs in the nutrient or in fatty tissues.

In order to prove the coccidiostatic activity increasing effect of the compound according to Example 3 it was compared with Salinomycin^{R} and Monensin^{R}. The infectedness of the animals was evaluated by 0, 1, 2, 3 crosses ($^{+}$, $^{++}$, $^{+++}$). The oocysta index consists of the sum of the crosses related to the total number of the animals.

Table 1

Diet	oocysta index	death	body weight	standard deviation
Infected control	30/10	2	145	41
Compound according to Example 3, 60 ppm 0 Salinomyin[x]	10/10	-	165	31
Compound according to Example 3, 30 ppm	30/10	3	141	27
Compound according to Example 3, Salinomycin, 120 ppm, 30 ppm	0/10	-	126	20
Compound according to Example 3, Salinomycin, 120 ppm, 15 ppm	0/10	-	141	20
Compound according to Example 3, Monensin[xx], 120 ppm, 30 ppm	0/10	-	144	25

[x] Hoechst
[xx] Eli Lilly

The table shows that in case of Salinomycin[R] the compound of Example 3 in a dose of 15 ppm gives the same protection, in case of Monensin the same compound at a dose of 30 ppm gives the same protection as the known compound administered per se at a dose recommended by the manufacturer.

The oocysta index is determined by a known method: the oocystas are counted microscopically. 25 visual fields are tested at the same time. If the number of the oocystas counted per field is below 1, then the value is marked by $^{+}$, if it is between 1-10, it is marked by $^{++}$, above 10 the value is marked by $^{+++}$.

Antioxidant activity

On the basis of active oxygen method (AOM)

1. Description of the method

Under thermostatic conditions a uniform stream of air is passed through the samples containing and not containing antioxidant. The change of Lea-number by time is measured.

2. Used materials

Glicerol trioleate purum $C_{57}H_{104}O_6$ LOBA FEINCHEMIE K.J. p. a.

Chloroform

Glacial acetic acid

$Na_2S_2O_3$ 0.002 N solution

Starch indicator

3. Test method

To 4 thermostated test cuvettes 30 g of glycerol trioleate are weighed in, in which 20 mg (0.02 %) test-antioxidant had been dissolved. The cuvettes are maintained at 70 °C and air is passed through the test oil at a velocity of 9.6-10 l/hour. Sample is taken every hour from the control and every 4 hour from the antioxidant samples and Lea-number is measured as follows:

To about 1 g sample 30 ml of a solution of an 1:1 chloroform and glacial acetic acid and 1 g solid potassium iodide is added, it is boiled for 60 sec, rapidly cooled and

15 ml of a 5 % aqueous potassium iodide solution is added.

It is titrated with 0.002 N $Na_2S_2O_3$ solution in the presence of a starch indicator.

$$\frac{\text{(Consumption/ml 0.002 N } Na_2S_2O_3\text{)-blank test x factor}}{\text{weighing in (g)}}$$

4. Results

4/1. control

Time (h)	1	2	3	4	5	6	7	8	9	10	11	12
Lea number	12.4	24.9	21.6	24.3	38.4	37.3	52.4	63.3	80.0	85.3	108	111

4/2. Samples

Time (h)	4	8	12	16	20	24	28	31	34
MTDQ comparative 6,6'-methylene-bis-derivative (Melting point 156 °C)	17.1	22.2	26.0	29.2	32.4	42.5	55.1	73.3	95.7
80 % material according to Example 2	20.2	19.3	18.6	25.2	29.4	36.6	44.5	58.4	64.9
98 % material according to Example 4	16.3	19.4	21.0	23.5	38.5	32.0	39.1	46.3	60.8
acetyl derivative according to Example 7	16.9	23.2	27.8	33.0	42.6	69.2	103.5		

In case of $X=SO_3Na$ a watersoluble antioxidant is obtained, which is tested in the following heterogeneous system:

30 ml water neutralized with 1 ml phosphate puffer of pH=7.

20 g glycerol trioleate, 1.5 g 30 % fatty alcohol sulponate.

20 g of the tested antioxidant agent are added to the emulsion thus prepared. The weighing in of the antioxidant and the Lea numbers are related to the oil content.

Lea number/time	0	2	4	6	8	10	12
Control	2.8	6.6	9.0	26.9	72.9	124.1	267.3
$SO^-{}_3Na^+$-derivative	2.8	3.7	6.1	10.9	28.0	45.0	93.7
Glutathion	2.8	3.3	4.7	9.1	16.3	34.1	51.6
L-ascorbic acid	2.8	8.8	32.6	69.6	103.0	132.0	193.0

EXAMPLES

Example 1

To four necked flask equipped with a stirrer and a thermometer, a feeding funnel and reflux 150 parts by weight of acetone containing 10 % water, 105 parts by weight of acetoanil, 2.5 parts by weight of pyridine are added and 100 parts by weight of concentrated hydrochloric acid is added dropwise. The mixture is heated to boiling point and stirred for 22 hours at this temperature. The mixture is cooled, whereafter 110 parts by weight of 40 % sodium hydroxide is added. The mixture is stirred under boiling, acetone is separated and 40 parts by weight of unreacted acetoanil are distilled off in vacuo. The buttom product is (60 parts by weight) of 2,2-di(2',2',4'-trimethyl-1',2'-dihydro-quinol-6'-yl)-propane of 80 % purity. Melting point: 125-135 ^{o}C.

Example 2

To an autoclave which can be heated by steam and cooled by water and equipped with a theremometer, stirrer and a feeding opening 100 parts by weight of acetonanil, 2 parts by weight of triethanol amine, 280 parts by weight of anhydrous acetone 106 parts by weight of concentrated hydrochloric acid are added. The equipment is closed and the content is stirred under pressure for 12 hours at 72-75 ^{o}C, then it is cooled to 40 ^{o}C and neutralized by adding 100 parts by weight of 40 % sodium hydroxide solution. The aqueous layer is removed and from the organic layer acetone is removed,

whereafter acetoanil is distilled off in vacuo. Yield: 62 parts by weight of 76 % 2,2-di(2',2',4'-trimethyl-1',2'-dihydro-quinol-6'-yl)-propane. Melting point: 120-135 °C.

Example 3

From the antioxidant according to Example 1 and 2 a product is obtained in a good yield which can be recrystallized from benzene, then from isopropanol, which melts at 156 °C, is completely white and the purity of which is 96 % according to HPLC chromatography. The product shows a biological activity similar to that of the product of purity 80 %. By evaporating the mother liquour an excellent rubber ageing inhibitor is obtained.

Example 4

One may proceed according to Example 1 but acetone is replaced by methyl ethyl ketone. Yield: 45 parts by weight of 2,2-di(2',2',4'-trimethyl-1',2'-dihydro-quinol-6'-yl)-butane, purity: 55 %. After recrystallization from hexane followed by isopropanol a product of purity 96-97 % is obtained melting at 117-118 °C. The product is an excellent antioxidant and its synergistic effect makes a 80 % saving possible when used together with coccidiostatics. From the mother liquour a non-colourizing antioxidant for rubber industry can be obtained.

Example 5

One may proceed as disclosed in Example 1 but as a ketone methyl isobutyl ketone is used. Yield: 20 % 2,2-di(2',2',4'-trimethyl-1',2'-dihydro-quinol-6'-yl)-isohexane. Purity: 50 %, melting point after recrystallization: 120-126 °C. The product can be used similarly like the product in Example 4.

Example 6

100 parts by weight of a 96 % product according to Example 3 are dissolved in 400 parts by weight of 96 % sulfuric acid, whereafter the mixture is slowly heated to 80 °C and the reaction is performed for 2-3 hours at this temperature. The sulfonated product is added dropwise to a mixture of 1000 parts by weight of water and 1000 parts by weight of ice and the precipitated sulfonic acid is filtered. It is recrystallized from hot water in the form of free acid and then converted to sodium salt. The thus obtained colourless crystalline product is dried to constant weight. Yield: 105 parts by weight.

Analysis of the product dried at 120 °C:

C 55.1 % (54.91); H (5.4 % (5.42); N 4.56 % (4.75); O 16.34 % (16.27) S 10.9 % (10.85); Na 7.7 % (7.8).

The product is suitable for therapeutical purposes.

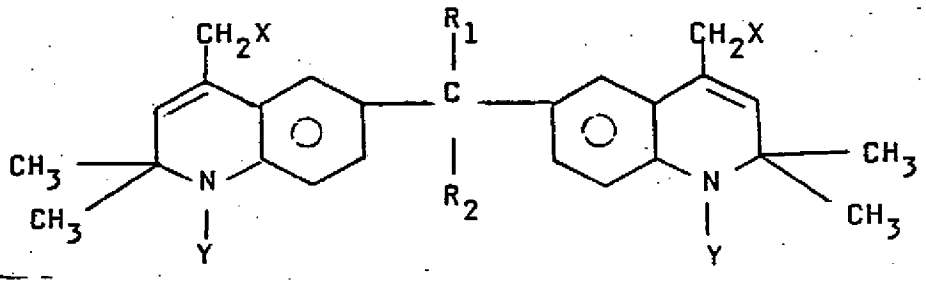
Example 7

The product of Example 3 is used. 100 parts by weight of this product are dissolved in 600 parts by weight of acetic

anhydride and the solution is heated for 2 hours under reflux. Acetic acid and the excess of the anhydride are distilled off from the crude product and it is recrystallized from 600 parts by weight of hot acetone. Yield: 114 parts by weight, melting point: 120-121 °C, and the product is obtained in the form of pale yellow crystals.

Claims:

1. Compounds of the general Formula I



and acid addition salts thereof - wherein

R^1 stands for optionally substituted C_{1-4} alkyl and

R^2 stands for optionally substituted C_{1-2} alkyl,

X stands for hydrogen or SO_3Me - wherein

Me stands for hydrogen, alkali or alkali earth metal ion,

Y stands for hydrogen or acyl.

2. Compounds as claimed in Claim 1

R^1 stands for optionally substituted C_{1-4} alkyl and

R^2 stands for optionally substituted C_{1-2} alkyl,

X stands for hydrogen and

Y stands for hydrogen.

3. Process for the preparation of the compounds of the general Formula I and acid addition salts thereof, which comprises condensing 2,2,4-trimethyl-1,2-dihydro-quinoline or a salt threof with a ketone of the general Formula R_1R_2CO - wherein R_1 and R_2 are as stated above - in the presence of a catalyst, such as mineral acid, preferably hydrochloric acid

and of a cocatalyst, such as nitrogen-containing base, preferably triethanol amine, pyridine or aniline in a solvent and if desired converting the obtained product to acid addition salt or setting free the base from the salt and if desired sulfonating and/or acylating the obtained base.

4. Process as claimed in Claim 3, which comprises performing the condensation in an 0-40 %, preferably 10-20 % of the ketone.

5. Process as claimed in Claim 3, which comprises using the acid preferably hydrochloric acid in a molar ratio of 0.9-2.5 mole, prefer ably 1.25-1.75 mole.

6. Pharmaceutical composition comprising as active ingredient a compound as claimed in Claim 1.

7. Fodder or fodder premix for the treatment of coccidiosis, which comprises a compound as claimed in Claim 2 next to ionophoric polyether antibiotics or salts thereof, preferably sodium salts.

INTERNATIONAL SEARCH REPORT

International Application No PCT/HU 88/00026

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) *

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[4]: C 07 D 215/06,215/08,215/12; A 61 K 31/47; A 23 K 3/00

II. FIELDS SEARCHED

Minimum Documentation Searched 7

Classification System	Classification Symbols
Int.Cl.[4]	C 07 D 215/06,215/08,215/12

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched 8

AT

III. DOCUMENTS CONSIDERED TO BE RELEVANT 9

Category *	Citation of Document, 11 with indication, where appropriate, of the relevant passages 12	Relevant to Claim No. 13
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A	DE, A1, 2 243 777 (MATERIAL VEG.) 22 March 1973 (22.03.73), see claims 1-3,6.	(1,3,6,7)

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IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
05 July 1988 (05.07.88)	12 July 1988 (12.07.88)
International Searching Authority	**Signature of Authorized Officer**
AUSTRIAN PATENT OFFICE	Pippan

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Anhang zum internationalen Recherchenbericht über die internationale Patentanmeldung Nr.

Annex to the International Search Report on International Patent Application No. PCT/HU 88/00026

Annexe au rapport de recherche internationale relatif à la demande de brevet international n°.

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		PL-B1- 125 177	30/04/1983
		PL-B1- 126 791	31/08/1983
		SE-A - 8 004 973	07/01/1981
		SE-B - 447 899	22/12/1986
		SE-C - 447 899	02/04/1987
		SU-A3- 990 083	15/01/1983
		SU-A1- 1 108 092	15/08/1984
		US-A - 4 356 306	26/10/1982
		US-A - 4 510 147	09/04/1985

			YU-A -	1 741/80	30/09/1983
DE-A1-2 243 777	22/03/1973		AT-B -	319 250	10/12/1974
-B2-	03/05/1978		AU-A1-	46 298/72	14/03/1974
-C3-	04/01/1979		BE-A1-	788 509	02/01/1973
			BG-D -	19 596	25/06/1975
			CA-A1-	992 546	06/07/1976
			CH-A -	580 079	30/09/1976
			CS-P -	170 505	27/08/1976
			DD-C -	101 667	12/11/1973
			DE-C2- 2	265 400	08/04/1982
			DE-C2- 2	265 399	04/10/1984
			DK-A -	441/75	04/08/1975
			DK-B -	135 990	25/07/1977
			DK-C -	135 990	27/12/1977
			DK-B -	149 332	05/05/1986
			DK-C -	149 332	24/11/1986
			ES-A1-	406 433	16/01/1976
			ES-A1-	435 497	16/04/1977
			ES-A5-	435 497	16/05/1977
			FR-A1- 2	154 469	11/05/1973
			FR-B1- 2	154 469	05/03/1976
			GB-A - 1	390 991	16/04/1975
			HU-P -	162 358	28/02/1973
			IT-A - 1	022 011	20/03/1978
			JP-A2-48	061 483	28/08/1973
			JP-B4-53-046	839	16/12/1978
			JP-A2-54-067	576	31/05/1979
			JP-B4-59-040	179	28/09/1984
			NL-A - 7	212 192	09/03/1973
			NL-B -	174 721	01/03/1984
			NL-C -	174 721	01/08/1984
			SE-A - 7	503 840	03/04/1975
			SE-B -	393 982	31/05/1977
			SE-C -	393 982	08/09/1977
			SE-B -	434 050	02/07/1984
			SE-C -	434 050	11/10/1984
			SU-D -	520 045	30/06/1976
			US-A - 4	025 631	24/05/1977
			US-A - 4	046 765	06/09/1977
			YU-A -	2 257/72	28/02/1982
			ZA-A - 7	205 777	26/09/1973